was obtained from a single tissue. Usually, both the (−)- and (+)-isomer of a single compound were tested on two tissues examined simultaneously. After maximum responses were obtained with each isomer of the selective agonists, (−)-isoproterenol, 10^{-7} M final bath concentration, was added and the effect produced by this treatment was taken as the maximum possible response which could be elicited through activation of the *beta* receptors. In experiments where cumulative dose-response curves were obtained with (−)-isoproterenol only, similar treatment neither increased nor decreased the already existing maximum response.

Prior to obtaining agonist-induced effects, tissues were exposed to various pretreatments in order to impede processes which could influence observed effects of the agonists (Furchgott, 1967, 1970). In most experiments, phentolamine, 10^{-5} M, was added 10 minutes before dose-response effects were obtained in order to block *alpha* adrenergic receptors. Although this treatment decreases the spontaneous atrial rate, it does not markedly alter potencies of *beta* receptor agonists or interfere with the establishment of beta receptor blockade in this tissue (Kroll and Patil, 1969; Buckner and Patil, 1971). The effects of the catecholamines, isoproterenol and trimetoquinol, were determined in the presence of tropolone, 10^{-4} M (30-minute contact), to inhibit the enzyme catechol-O-methyltransferase.

In some experiments, the effect of phenoxybenzamine, 10^{-6} M, on agonist-induced responses was examined by exposing the tissues to this compound for 30 minutes, followed by seven complete changes of the bath with fresh physiologic salt solution during the next 15-minute period. Fifteen minutes after the final wash, cumulative addition of a *beta* receptor agonist was begun in atria or carbachol was added to tracheal strips. Since release of endogenous norepinephrine, as produced by phenoxybenzamine (Furchgott, 1966), may influence observed effects of direct-acting agonists (Trendelenburg, 1968), tissues used in these experiments were taken from guinea pigs which had been pretreated with reserpine (5 mg/kg i.p.) 16 to 24 hours previously. In addition to irreversible *alpha* adrenergic receptor blockade (Tuggle, 1968), phenoxybenzamine also blocks the adrenergic neuronal membrane uptake mechanism (Furchgott, 1966) as well as the extraneuronal uptake process and, hence, the influence of catechol-O-methyltransferase on externally applied catecholamines (Eisenfeld *et al.*, 1967).

Competitive antagonism of the effects of *beta* receptor agonists was produced by exposing the tissues to (−)-sotalol, 3×10^{-5} M, for 1 hour prior to obtaining cumulative dose-response effects of the agonists. Control dose-response curves were obtained from the paired tracheal strips or simultaneously examined right atria.

Potencies of the enantiomers are expressed as negative log molar ED50 values when responses produced by each concentration of agonist were calculated as a percentage of the final maximum response elicited by that isomer. Potency differences between enantiomers were obtained by subtracting negative log ED50 values. Because of a limited supply of (+)-salbutamol, final maximum responses in atria could not be obtained from this agonist. Therefore, atrial responses produced by each concentration of the isomers of salbutamol were calculated as a percentage of the final maximum response elicited by subsequent addition of (−)-isoproterenol. The potency difference between enantiomers of salbutamol in atria was determined from approximately parallel portions of the dose-response curves (20% of the isoproterenol-induced maximum).

Standard errors of the mean were calculated for all samples and 95% confidence intervals (C.I.) for potency differences between enantiomers.

Chemical structures of the newer agonists used in this study are shown in figure 1. All drug solutions were prepared on the day of each experiment and were kept refrigerated until shortly before use. Dilutions of the agonists were made from 10^{-2} M refrigerated stock solutions prepared in 0.9% saline with 0.05% sodium metabisulfite. Other drugs were prepared in 0.9% saline and molar strengths are expressed in terms of final bath concentrations.

The following drugs were used: (−)- and (+)-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline HCl (trimetoquinol); (−)-, (+)- and (±)-2′-hydroxy-5′-(1-hydroxy-2-isopropylaminoethyl)methanesulfonanilide

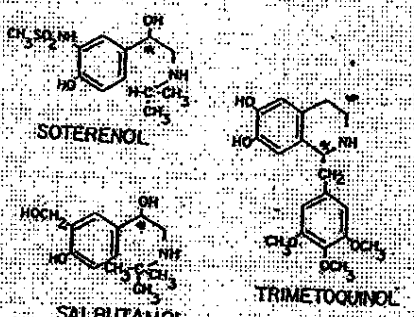

FIG. 1. Chemical structures of tissue selective *beta* receptor agonists used in the present experiments. Asterisk denotes position of the asymmetric carbon atom.

HCl (soterenol); (−)- and (+)-2-t-butylamino-1-(4-hydroxy-3-hydroxymethyl)phenylethanol acetate monomethanolate (salbutamol); (−)-1-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide HCl (sotalol, MJ 1999); (−)-isoproterenol-(+)-bitartrate dihydrate; carbachol chloride (Aldrich Chemical Company, Inc., Milwaukee, Wisc.); tropolone (Aldrich); phentolamine HCl (Ciba Pharmaceutical Company, Summit, N.J.); phenoxybenzamine HCl (Smith Kline and French Laboratories, Philadelphia, Pa.) and reserpine (Serpasil, Ciba). The signs (−) and (+) refer to the direction of rotation of polarized light, *laevo* and *dextro*, respectively. The sign (±) refers to the racemic mixture. The same samples of isomers of the agonists were used for the entire study.

Specific rotations of the isomers of trimetoquinol and soterenol, dissolved in ethanol, were determined by optical rotatory dispersion using a Cary 60 spectropolarimeter. Calculated specific rotations from the plain dispersion curves for (−)- and (+)-trimetoquinol were −111.5 (307.5 nm) and +101.4 (307.5 nm) and for (−)- and (+)-soterenol, −197 (297.5 nm) and +218.2 (297.5 nm), respectively. These values indicate the similar degree of resolution of both isomers of the same compound.

Results

Potencies of enantiomers of selective agonists. Dose-response curves obtained from cumulative administration of the optical isomers of soterenol to isolated atria and trachea are shown in figure 2. Potency differences between the isomers are indicated by the numbers between the horizontal arrows. Data from these and other isomers are summarized in table 1.

Even though potencies of single isomers may differ as much as 24-fold (for salbutamol) between atria and trachea, for a given pair of isomers, the stereoselectivity for production of responses in the two tissues is the same. The maximum difference in enantiomeric potency ratio between the tissues is about 2-fold (0.33 log unit).

Combined reserpine and phenoxybenzamine pretreatment did not change the potency difference observed between the isomers of soterenol in either tissue (table 1). However, from both tissues, these treatments resulted in parallel shifts to the left of the dose-response curves for

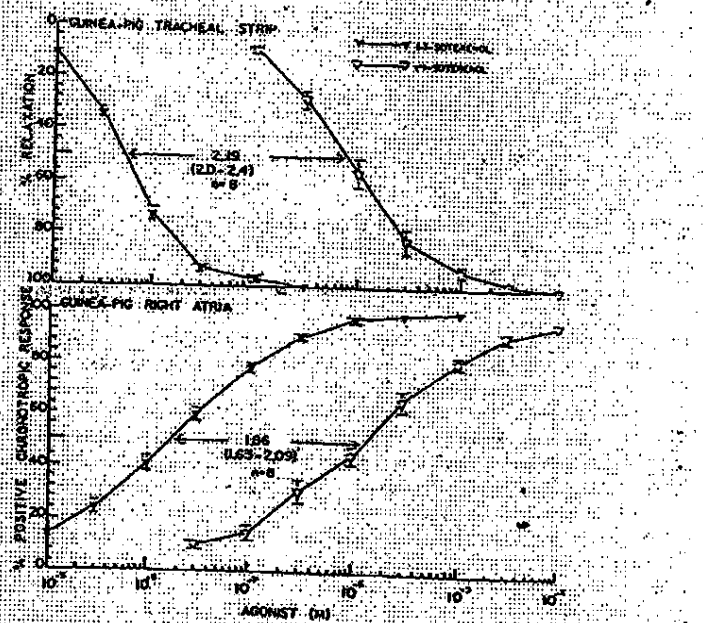

FIG. 2. Log dose-response curves for (−)- and (+)-soterenol obtained in atria and trachea taken from normal guinea pigs. Numbers between the horizontal arrows connecting the curves are enantiomeric potency differences in log units with 95% C.L. in parentheses. *n* = number of observations. All curves were obtained in the presence of phentolamine. Vertical lines indicate S.E.M.

TABLE 1

Effects of beta adrenergic receptor agonists on guinea-pig atria and tracheal strips

Agonist	Isolated Guinea-Pig Right Atria				Isolated Guinea-Pig Tracheal Strip			
	−log molar ED50 with S.E.M.	% maximum with S.E.M.	n[e]	Enantiomeric potency difference[d] (99% C.L.)	−log molar ED50 with S.E.M.	% maximum	n[e]	Enantiomeric potency difference[d] (99% C.L.)
Normal tissue[a]								
(−)-Isoproterenol	8.70 ± 0.06		8		9.13 ± 0.07		8	
(−)-Soterenol	7.75 ± 0.07	65 ± 3	8	1.36	8.30 ± 0.03	100	8	2.19
(+)-Soterenol	5.92 ± 0.09	44 ± 2	8	(1.03–2.09)	6.10 ± 0.04	100	8	(2.0–2.4)
(±)-Soterenol	7.29 ± 0.07	60 ± 2	10		8.11 ± 0.04	100	6	
(−)-Trimetoquinol	8.68 ± 0.05	91 ± 1	8	1.61	9.63 ± 0.05	100	9	1.58
(+)-Trimetoquinol	7.07 ± 0.07	33 ± 1	8	(1.43–1.79)	8.08 ± 0.06	100	9	(1.33–1.79)
(−)-Salbutamol	(7.70 ± 0.13	73 ± 3	6	2.20	(8.61 ± 0.08	100	6	2.46
(+)-Salbutamol	5.42 ± 0.06		6	(1.91–2.60)	6.07) ± 0.07	100	6	(2.22–2.70)
Reserpine-pretreated tissue[f]								
(−)-Isoproterenol					9.26 ± 0.06		6	
(−)-Soterenol	8.13 ± 0.08	69 ± 2	9	1.35	8.99 ± 0.05	100	7	2.25
(+)-Soterenol	6.93 ± 0.06	54 ± 1	9	(1.04–2.07)	6.74 ± 0.11	100	6	(1.99–2.52)

[a] Tissues were exposed to tropolone and phentolamine. Tropolone was not used with isomers of soterenol and salbutamol. See "Methods."

[b] Negative log of the concentration of each agonist required to produce 50% of its own maximum effect. For the isomers of salbutamol, values represent negative log of the concentrations required to produce 20% of the maximum effects of (−)-isoproterenol.

[c] Maximum effect of each agonist calculated as a percentage of the maximum response produced by (−)-isoproterenol. See "Methods."

[d] n, number of observations.

[e] Enantiomeric potency difference = [(−log ED50 of (−)-isomer) − (−log ED50 of (+)-isomer)]. Values for salbutamol in atria calculated using concentrations required to produce 20% of the maximum effects of (−)-isoproterenol.

[f] Tissues were exposed to phenoxybenzamine and washed. See "Methods."

each isomer. Slight potentiation of the effects of isoproterenol was also observed in trachea. Slight alteration of responses to soterenol by phenoxybenzamine suggests that phenoxybenzamine-sensitive adrenergic neuronal or extraneuronal accumulation may play a small role in determining the tissue distribution of this agonist.

Data from untreated atria show that the various procedures do not markedly alter the potency difference between isomers of soterenol in this tissue. In the absence of any pretreatment of atria, −log molar ED50 values for (−)- and (+)-soterenol were 8.07 ± 0.13 (S.E.M., n = 10) and 5.94 ± 0.22 (n = 9) while maximum effects were 65 ± 1 and 54 ± 3% of the maximum effects produced by isoproterenol, respectively.

Results from (±)-soterenol are included in table 1 as a means of comparison with the resolved isomers. Potencies of the racemate are 2 to 3 times less than those of the (−)-isomer. In atria, the maximum positive chronotropic effect produced by the racemate is also slightly less than that produced by the (−) form.

Responses produced by the isomers of selective agonists developed more slowly than those produced by isoproterenol. In both tissues, maximum effects to individual concentrations of isoproterenol usually occurred within 3 to 6 minutes after addition to the bath. This time interval was 5 to 12 minutes for the isomers of soterenol and salbutamol and 12 to 15 minutes for the isomers of trimetoquinol.

Regardless of the difficulties involved in interpretations, when potencies (−log molar ED50 values) of the (−)-isomers of the selective agonists are compared with those of (−)-isoproterenol (fig. 3), relative differences between the in-

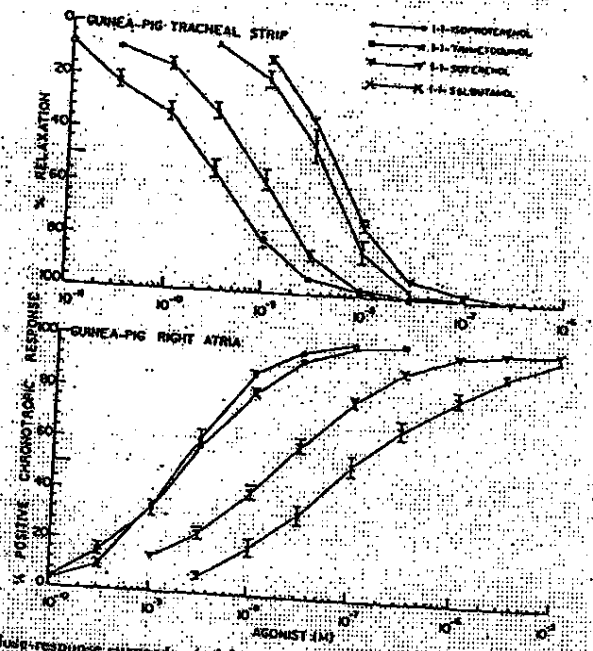

FIG. 3. Log dose-response curves for (—)-isomers of isoproterenol, sorerenol, trimetoquinol and salbutamol obtained in atria and trachea taken from normal guinea pigs. See "Methods" for details on drug incubations. Percent response for each agonist concentration was calculated as a percentage of the maximum response produced by that agonist. Vertical lines indicate S.E.M.

ases are apparent only in the case of salbutamol. (—)-Salbutamol is 44 and 3 times, while (—)-sorerenol is 3.5 and 1 times less potent than (—)-isoproterenol in atria and trachea, respectively. The (—) form of trimetoquinol is equally potent in atria and 3 times as potent in trachea as (—)-isoproterenol.

However, as illustrated in figure 1, these agonists are better classified as "partial agonists" in the heart since slopes of the dose-response curves and maximum positive chronotropic effects are less than those of isoproterenol. If "activities" are compared, *i.e.*, concentrations required to produce 50% of the maximum effect of isoproterenol, salbutamol is 140 times and sorerenol 46 times less active than isoproterenol in atria. Trimetoquinol is approximately equal in activity to isoproterenol since these agonists produce similar maximum responses.

Antagonism by sotalol. The effects of (—)-sotalol, 3×10^{-4} M, on responses to the isomers of sorerenol and (—)-isoproterenol are shown in Table 2. As previously demonstrated (Buckner and Patil, 1971), sotalol is a more potent beta receptor antagonist in trachea. Furthermore, in trachea, sotalol produces comparable degrees of antagonism of the effects of all agonists examined. However, sotalol is selective in blocking effects of the isomers of sorerenol in atria. In experiments on atria, the shifts of trimetoquinol dose-response curves produced by sotalol were (in log units) 1.05 ± 0.16 ($n = 3$) against the (—)-isomer and 0.98 ± 0.09 ($n = 3$) against the (+)-isomer. The antagonism exerted by sotalol in both tissues was presumed to be competitive in all cases since the dose-response curves were shifted to the right in parallel fashion.

Discussion

A crucial experimental criterion in the differentiation and identification of adrenergic receptors is stereochemical selectivity (Patil, 1969). Under proper experimental conditions, similar receptor types should exhibit similar stereoselec-

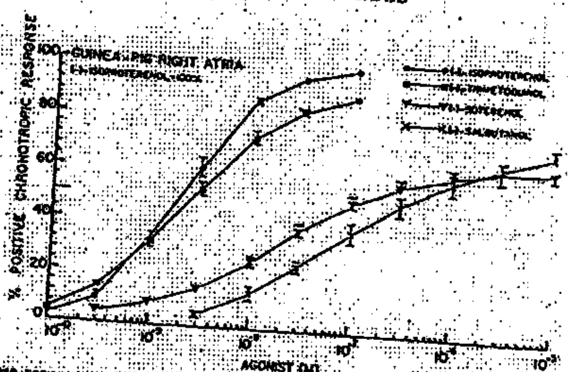

FIG. 4. Log dose-response curves for (−)-isomers of isoproterenol, soterenol, trimetoquinol and salbutamol obtained in atria taken from normal guinea pigs. See "Methods" for details on drug incubations. Percent response for each agonist concentration was calculated as a percentage of the final maximum response produced by addition of (−)-isoproterenol to each tissue. Vertical lines indicate S.E.M.

TABLE 2

Antagonism of effects of beta adrenergic receptor agonists by (−)-sotalol in guinea-pig atria and tracheal strips

Agonist	Isolated Guinea-Pig Right Atria[a]		Isolated Guinea-Pig Tracheal Strip[a]	
	Log shift with S.E.M.[b]	n[c]	Log shift with S.E.M.[b]	n[c]
(−)-Isoproterenol	0.92 ± 0.05	7	1.21 ± 0.04[d]	5
(−)-Soterenol	1.38 ± 0.11	5	1.28 ± 0.05[d]	5
(+)-Soterenol	1.32 ± 0.10	7	1.70 ± 0.09	4

[a] Tissues were exposed to [illegible] and [illegible]. [illegible] was [illegible] with isomers of [illegible]. See "Methods."
[b] Log shift = (−log molar ED50 without antagonist) − (−log molar ED50 with antagonist). In [illegible] experiments, log shift of dose-response curves for (−)- and (+)-soterenol was determined at 30 and 50%, respectively, of the maximum response produced by isoproterenol. Concentration of antagonist was 3 × 10^{-5} M.
[c] n, number of paired or unpaired observations.
[d] Values taken from Buckner et al. (1971).

tive interactions with agonists and antagonists. Like optical isomers of classical catecholamine agonists and competitive antagonists, isomers of newer, selective *beta* receptor agonists interact with *beta* receptors of guinea-pig atria and trachea in very similar fashion. In other words, potency differences between the enantiomers are similar in the two tissues regardless of the position of the dose-response curves along the log dose axis. For example, even though (−)-trimetoquinol is 10 times more potent in trachea than atria, the (+)-isomer exhibits the same degree of tissue selectivity. The present observations from potencies of enantiomers of selective agonists support the suggestion that *beta* receptors of guinea-pig atria and trachea may be similar (Buckner and Patil, 1971).

The agonist action of trimetoquinol adds new dimensions to structure-activity investigations of *beta* receptors. Whereas other agonists possess a center of asymmetry at the *β* carbon atom of the phenethanolamine structure, trimetoquinol is a cyclized derivative with no substitution at the site corresponding to the *β* hydroxyl. These differences suggest that it combines with additional receptor regions and interacts at an alternative asymmetric site on the receptor. The similar potency differences for trimetoquinol in atria and trachea suggest the similarity of these sites and strengthen the suggested similar nature of the receptor sites in the two tissues.

A major assumption associated with the use of optical isomers to differentiate receptors is that responses to the lesser active isomer are not entirely due to contamination of the sample by the more active isomer. Even though similar specific rotations from optical rotatory dispersion measurements (see "Methods") suggest similar degrees of resolution of the isomers of soterenol and trimetoquinol, in the absence of a pure standard the degree of impurities in each sample can not be determined. However, absolute stereochemical purity, although desirable, is not essential in the pharmacologic experiments provided that the same chemical samples are used in all studies and that the less active (+)-isomers

do not have zero potency. At least one indirect line of evidence suggests that (+)-isomers of adrenergic drugs possess their own effects. In most cases, it has been shown that (+)-isomers are equal in potency to the corresponding desoxy derivatives (Patil *et al.*, 1970). This relationship is predicted by the Easson and Stedman hypothesis (1933) that (+)-isomers act as if the alcoholic OH were missing since this group, by being oriented away from the receptor, would not contribute to the affinity of the molecule for the receptor. The desoxy derivative of soterenol has equal potency to (+)-soterenol in guinea-pig trachea and rat uterus (Dr. G. R. McKinney, personal communication) and, therefore, conforms to this hypothesis. This allows the assumption that the effects produced by (+)-soterenol are elicited mainly by that isomer. The desoxy derivative of salbutamol has not been tested and the hypothesis may not now be applied to trimetoquinol.

Farmer *et al.* (1970a) and Brittain *et al.* (1970) reported that racemic forms of soterenol, salbutamol and trimetoquinol were, respectively, 3.3, 500 and >10,000 times less potent in guinea-pig atria and 5, 5 and 7 times less potent in guinea-pig trachea than isoproterenol. Regardless of the manner in which the values are obtained, our data do not reveal such largely different relative potencies for salbutamol and trimetoquinol between the two tissues. In our experiments, salbutamol exhibited greater selectivity than trimetoquinol and soterenol which, under most experimental conditions, were minimally selective for trachea. More recently, Brittain *et al.* (1973) reported a difference in potency between isomers of salbutamol in isolated guinea-pig trachea which is approximately one-fourth the value obtained in our experiments. Furthermore, they were unable to demonstrate appreciable positive chronotropic effects in guinea-pig right atria using either isomer. In both tissues, effective concentrations of the isomers appear to be about 100 times greater than in our experiments. As outlined by Furchgott (1967), one of the experimental conditions which must be satisfied in analyzing drug-receptor interactions is that sufficient time be allowed for steady-state responses to develop after addition of each drug concentration. The selective agonists have slower rates of onset of action than isoproterenol and, unless this factor is considered in studying pharmacologic effects, a highly potent agonist could appear less potent. In addition, *alpha* adrenergic receptor activation by these compounds could interfere with observed *beta* receptor potency and this factor can be eliminated by addition of an *alpha* receptor antagonist.

Even under appropriate experimental conditions of the present study, salbutamol, soterenol and, to a lesser degree, trimetoquinol could be classified as "partial agonists" in atria. This could account for some of the reported selectivity when "activities" rather than "potencies" are evaluated. Since activity measures the concentration required to produce 50% of the maximum response to a standard agonist, this parameter for a partial agonist like salbutamol would be determined in the upper portion of the dose-response curve where the slope is diminishing. The potency of an agonist is measured in the steep portion of the dose-response curve (at 50% of the maximum produced by that agonist) and is expected to more accurately reflect receptor binding. The lesser relative activity of the agonist-induced effects in only atrial preparation could be related to 1) different degrees of receptor reserve (Ariens, 1964), 2) greater desensitization during cumulative drug addition, 3) non-competitive action beyond receptor activation and or 4) different degrees of access to receptor sites.

Regardless of the interpretation, decreased ability of an agonist to produce a response in one tissue as opposed to another does not provide compelling evidence that the receptor binding sites in the two tissues are different. Although similar stereochemical selectivity for agonist activity in two tissues is not absolute proof that the binding sites are the same, it is one of the criteria which must be used in receptor classification.

Effects of agonists acting on the same receptor should be blocked to the same extent by a competitive antagonist (Arunlakshana and Schild, 1959). However, it has been argued that different degrees of blockade by the same antagonist in two tissues does not necessarily suggest a difference of receptor type in those tissues (Buckner and Patil, 1971; Buckner and Christopherson, 1971). Hence, there are alternative means of explaining selectivity for trachea exerted by sotalol in our experiments. However, selective blockade by sotalol of effects of the isomers of soterenol in guinea-pig atria is not explained on

the basis of these considerations. Carlsson *et al.* (1972) demonstrated a similar phenomenon in cat atria and suggested the possibility that there is an array of binding modes on the receptor such that structurally varied agonists would not necessarily interact with the same configuration of the receptor. According to this model, an antagonist could also selectively bind to one of these sites. The close structural similarity between sotalol and soterenol suggests that they combine with similar sites. However, are these the exact sites with which isoproterenol interacts? In trachea, sotalol does not exert selective blockade of the different agonists. On the basis of enantiomeric potency differences reported for several agonists and antagonists, the *beta* receptors of guinea-pig atria and trachea may be similar. Therefore, an explanation for selective blockade of agonists in only atria should be sought in events not involving differences in the specific receptors. For example, a partial agonist like soterenol also acts as a competitive antagonist (Ariens, 1964; Raper and Malta, 1973) and may produce additive antagonism during cumulative drug addition. Alternatively, isoproterenol may have additional means of producing responses which could not be blocked by a specific receptor or antagonist. An interesting possibility is that inhibition of phosphodiesterase by catecholamines may contribute to mechanical produced by these compounds (Goren and Rosen, 1972; Hitchcock, 1973). The several possibilities should be explored in quantitative fashion before making conclusions about ligand binding modes on the receptor.

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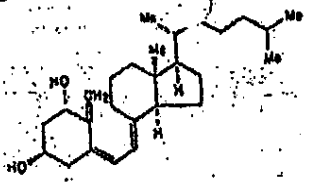
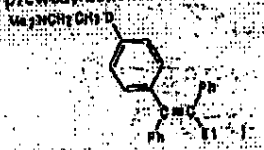


2 wk of *3-deoxy-1α-hydroxycholecalciferol* [53964-32-8] 16 and 64 μg daily for 1 wk of *24R,25-dihydr[illegible]cholecalciferol* [21-11-4] proved ineffective. In 32 successfully transplanted ents, restoration of normal or near normal renal function rum creatinine <1.9 mg/100 mL) was not always followed by immediate improvement in active Ca absorption. Ca rption, esp. in female patients, was adversely affected by the uired immunosuppressive *prednisone* [53-03-2] therapy and provement was slow.

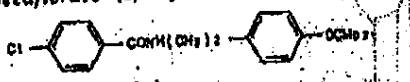
89: 123258k Effect of tamoxifen pre-treatment on the ention of tritiated estradiol and 5α-dihydrotestosterone d on glucose metabolism in human breast carcinomas. hepande, N., Mitchell, Irene, Hughes, D. (Imp. Cancer Res. nd., London, Engl.). *Eur. J. Cancer* 1978, 14(5), 473-7 (Eng). The effect of pretreatment with *tamoxifen* (I) [10540-29-1] on *glucose* [50-99-7] metab. and the retention of injected *estradiol-17β* [50-28-2] and *5α-dihydrotestosterone* [521-18-6] ly human breast carcinomas were studied in patients undergoing mastectomy. The pretreatment reduced retention of estradiol-17β, whereas a small but significant rise in 5α-dihydrotestosterone accumulation was obsd. There was an increase in both phosphofructokinase and glucose-6-phosphate dehydrogenase activities in tumors from treated patients, whereas α-glycerol-phosphate dehydrogenase activity was significantly reduced in the same tumors. These changes in carbohydrate metab. may not be due to the blocking of hormone receptors.



89: 123259m Comparison of acute bronchodilator effects of oral salbutamol, salbutamol + hydroxyzine and ephedrine + theophylline + hydroxyzine combinations in asthmatic [illegible]. Multari, A.; Ahonen, A. (Dep. Pulm. Dis., Tampere [illegible] Hosp., Pitkaniinna, Finland). *Curr. Ther. Res.* 1978, [illegible] Sect. 1), 587-74 (Eng). The bronchodilator effects of oral *salbutamol* [18559-94-9], the *hydroxyzine-salbutamol* mixt. [67650-17-8], and *ephedrine-hydroxyzine-theophylline* mixt. [55451-77-7] were obsd. in an acute study of asthmatic patients. All 3 drug combinations were able to increase peak expiratory flow (PEF) rates. The effect of oral salbutamol (4 mg) both alone and in combination with hydroxyzine (10 or 20 mg) was faster than the effect of the ephedrine-hydroxyzine-theophylline mixt., but the effect of the ephedrine-hydroxyzine-theophylline mixt. perhaps lasted longer. A second dose of the above ephedrine combination and the hydroxyzine-salbutamol mixt. given 5 h after the first dose was still able to increase the PEF rates. This was possibly an indication of the cumulative effect of the ephedrine-hydroxyzine-theophylline mixt., which was not so clearly seen with the salbutamol combinations. Otherwise, there were no differences between the effects or side effects of the drugs investigated in the present study. A combination of salbutamol and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixt. but still about the same effectiveness. The dose of 10 mg of hydroxyzine had in combination about the same effect as 20 mg, but drowsiness was obsd. less frequently with the smaller dose.

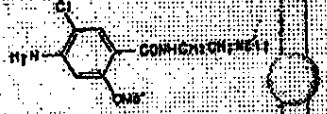
89: 123260e Changes in gastric secretion following administration of preparations affecting the parasympathetic and sympathetic nervous system. Abasov, I. T.; Ior, I. M. [illegible] Azerbaijan Res. Inst. Radiol. [illegible] Cent., Azerbaijan [illegible] 1978.

phen[illegible]coumon, Zimmermann, K.; [illegible] Hoffri[illegible]r, A.; Lang, P. D.; Andrassy, K.; Se Clin. Pharmacol., Med. Universitatsklin. Heidel Ger.). *Atherosclerosis.* (*Shannon, Irel.*) 1978 (Eng). *Bezafibrate* (I) [41859-67-0] give



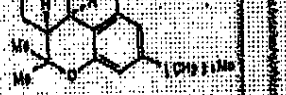
hyperlipemia on long-term treatment with racemi [456-97-2] increased the anticoagulant respons drug. Treatment with I at 450 and 600 mg rsdn. of the phenprocoumon dose by 18.5 Correspondingly, the serum level of phenopro by 11.8 and 35.3%. No evidence for an altere of racemic phenprocoumon was found during Apparently, I and analogous hypolipemic d response to oral anticoagulant drugs by increas the receptor site for coumarins or the rate vitamin-K-dependent clotting factors. The fibripolytic enzyme system demonstrated a fibrinolytic activity by enhancing the activity activator. The lysis time for euglobulin significantly, plasma fibrinogen only moderately activity was not altered substantially by a decrea [9041-93-3] and a slight increase of α2-M contrast with the inhibition of platelet functio the fibrinolytic enzyme system showed no dos

89: 123262g Influence of hyperprolactinemia on gonadal function in m clopramide on gonadal function in. Conti, C.; Frajese, G.; Sciarra, F.; Rocco, A.; Conti, G. Univ., Rome, Rome, Italy). *Clin. Endocrin.* 8(5): 427-33 (Eng). In 5 male volunteers giv



(I) [364-62-5] 10 mg three times daily [9002-62-4], concns. were elevated in the testosterone and cortisol concns. were not was obsd. in LH or FSH response to LH pretreatment values. A redn. in seminal count were obsd. in each subject. Four decrease in libido and 3 lost spontaneous I-induced hyperprolactinemia could be the changes in semen and erectile activity, the blocking drug might directly affect re mechanism of erection, the testis or accessor

89: 123263h Bronchodilator effect of [illegible] binol. Hartley, J. P. R.; Nogrady, S. G.; J. D. P. (Asthma Res. Unit., Sully Hosp., *J. Clin. Pharmacol.* 1978, 5(6), 323-5 (Eng).



hydrocannabinol (I) [1972-08-3] produc asthmatic patients. Administered in 60 50–200 μg by inhalation from an aero judged to be in a steady state, it increase rate and forced expiratory vol. in 1 s. magnitude, and duration of the bronch related.

89: 123264j Methylphenidate and sex [illegible] Janowsky, David S.; Leichner, Pierre; Lewis, Huey, Leighton, Clopton, Paul (C California Med. Sch., La Jolla, Calif.) *(Berlin)* 1978, 58(1), 49-7 (Eng). In s

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
9207363.4

Relevant Technical fields

(i) UK Cl (Edition K) A5B (BHA, BJA)

(ii) Int Cl (Edition 5) A61K

Search Examiner

J F JENKINS

Databases (see over)
(i) UK Patent Office

(ii) ONLINE DATABASE: DIALINDEX (MEDICINE), CAS-ONLINE

Date of Search

6 AUGUST 1992

Documents considered relevant following a search in respect of claims 1 TO 10

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X,E	WO A1 91/09596 (SEPRACOR INC) whole document	1-3, 5-9
X,E	EP A1 0455155 (BOEHRINGER INGELHEIM)	1-3, 5-9
Y	Chem. Pharm. Bule. 26(4), 1123-9, (1976) Murase et al	1-3, 5-9
Y	J. Med.Chem. 14(9), 895-6 (1971) Hartley et al	1-3, 5-9
Y	J. Liq. Chromatogr.11, 2147-63 (1988) Okamoto et al	1-3, 5-9
Y	Biochem. Pharmacol. 35(12), 1981-5, (1986) Köster et al	1-3, 5-9
	Br. J. Clim. Pharmac. 27, 49-56, (1989) Borgstrom et al	1-3, 5-9

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DLEV011881

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner:

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, office of Special Program Examiner, Crystal Park 1, Suite 520, Washington, D.C. 20231, December 21, 1994.

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Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: December 21, 1994

To: Hon. Commissioner of Patents and Trademarks
Office of Special Program Examiner
Crystal Park 1
Suite 520
Washington, D.C. 20231

Petition To Be Accorded A Filing Date Under 37 C.F.R. 1.181

Dear Sir:

Applicants undersigned agent respectfully petitions the Commissioner of Patents and Trademarks to accord the above-identified application the filing date of November 7, 1994. This petition is presented within five (5) days of the discovery of the incomplete application filed under 37 C.F.R. 1.60. The circumstances surrounding the filing of the continuation application are as follows:

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December 21, 1994

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DLEV011883

Application serial number 08/163,581 was filed on December 7, 1993. It was a continuation of application serial 07/896,725 filed June 9, 1992 which was in turn a continuation of U.S. application serial number 07/461,262 filed January 5, 1990. After amendment of the claims, application serial number 08/163,581 was allowed on July 26, 1994 and the issue fee was paid on August 3, 1994.

On November 7, 1994, applicants filed a continuing application under 37 C.F.R. 1.60 with the intent of continuing prosecution of some of the subject matter that had been amended out of the parent case 163,581. The continuing application was sent by express mail under 37 C.F.R. 1.10 and was stamped in the U.S. Patent and Trademark Office mail room on November 7, 1994, and given a serial number of 08/335,480. A copy of the returned postcard is enclosed as Exhibit A.

On November 8, 1994, the parent application 08/163,581 issued to U.S. Patent 5,362,755. A copy of the patent is enclosed herewith as Exhibit B.

On December 19, 1994, applicants undersigned representative received a Notice of Incomplete Application filed under 37 C.F.R. 1.60; the notice was mailed from the Patent and Trademark Office on December 16, 1994. A copy of the notice is enclosed herewith as Exhibit C. The notice indicated that the specification as filed on November 7, 1994, was missing pages 2 and 3. Applicants undersigned representative has examined the file copies of material sent to the Patent and Trademark Office and the postcard returned from the USPTO, and on that basis believes that the application was probably filed with pages 2 and 3

inadvertently missing. Upon receipt of the Notice of Incomplete Application, the undersigned expeditiously (1) returned a copy of the Notice of Incomplete Application and a copy of the Response thereto (Exhibit D) and a copy of the missing pages (Exhibit E) to the Application Processing Division; and (2) filed this Petition with the appropriate fee.

Applicants suggest that, although the copy of the application filed on November 7, 1994, may have, in fact, been missing pages 2 and 3, neither the public interest nor the U.S. Patent and Trademark Office have been compromised by this inadvertent error. On the other hand, if the filing date of November 7, 1994, is not granted, applicants' rights to continue prosecution of unclaimed subject matter will be seriously compromised. Applicants believe that the public interest and the USPTO's oversight thereof would not be compromised for the following reasons: (1) The U.S. Patent and Trademark Office had in its possession on November 7, 1994, the full and accurate text of the two missing pages; these pages were found in the parent application 08/163,581 which was pending on November 7 and which was cited in the Division-Continuation Program Application Transmittal Form submitted with the instant application. A copy of the Transmittal Form is enclosed as Exhibit F; (2) The materials filed on November 7, 1994, had they been filed as a regular application (as opposed to under Rule 1.60) would have been accorded a filing date of November 7 because they contained, as required by law, a specification, at least one claim, and an indication of inventorship. In addition, although not required for a filing date, they contained a check in the amount of $365 to cover the filing fee.

Inasmuch as no harm would come to the public by virtue of granting of this petition, and inasmuch as great harm would come to applicants by denial thereof, applicants request that the filing date of November 7, 1994, be accorded the above application.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: December 21, 1994

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